

### REMARKS

Claims 1-78 are pending in the application. Claims 1-6, 9-14, 17-22, 25-31, 34-39, 42-47, 50, and 73-77 are under active consideration, claims 7, 8, 15, 16, 23, 24, 32, 33, 40, 41, 48, 49, 51-72, and 78 having been withdrawn as drawn to non-elected subject matter. By the present communication, claims 1, 20, 26, 45, and 73 have been amended. In view of these amendments, claims 10, 12, 18, 19, 35, 37, 43, and 44 have been canceled herein without prejudice or disclaimer. Subsequent to the entry of the present amendment, claims 1-6, 9, 11, 13, 14, 17, 20-22, 25-31, 34, 36, 38, 39, 42, 45-47, 50, and 73-77 will remain under active consideration. These amendments add no new matter as the claim language is fully supported by the specification and original claims.

#### **I. Rejections under 35 U.S.C. §112, First Paragraph (written description)**

Claims 1-, 9-14, 17-22, 25-31, 34-39, 42, 47, 50, and 73-77 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants note that this rejection as applied to claims 10, 12, 18, 19, 35, 37, 43, and 44 has been rendered moot by the cancellation herein of these claims. Applicants respectfully traverse this rejection as it applies to the pending claims.

Specifically, the Examiner asserts that the claims “recite that the modified MHC monomer has bound thereto a template MHC binding peptide, but do not recite functional properties of the binding, nor which biological activity/ies of the non-modified MHC molecule(s) are retained” (Office Action at pages 3-4, bridging paragraph).

To the contrary, the claims as presently amended require both structural and functional properties of the “modified MHC monomer.” The MHC monomer is further defined as an HLA-A2 molecule further comprising a beta-2 microglobulin which, when modified is further required to retain the ability to assemble into a ternary complex with the template MHC-binding peptide and beta-2 microglobulin. Thus, the embraced modified MHC monomer are defined with respect to structure, that of HLA-A2 bound to

beta-2 microglobulin and template peptide, the structure of which was well-known in the art at the time of filing. Further, since this structure was well-known in the art, Applicants are not required to reproduce that information in the present application. Indeed, in Capon v. Eshhar, 76 U.S.P.Q.2d 1078, 1085, 418 F.3d 1349, at 1357 (Fed. Cir. 2005), the court reasoned that when the prior art includes structure and function information, there is no *per se* rule that the information must be determined afresh. As in Capon, the present invention is not in the discovering of which MHC monomers or binding peptides of some unknown or “wished for” sequence might be related to a specific function, but in the novel combination of the element of known components to achieve a novel result (Id., at 1357), that is, a method for identifying MHC-binding peptides. Thus, in concurrence with the Court of Appeals for the Federal Circuit in Capon, Applicant submits that the requirement that a method utilizing polypeptides prepared from known sequences of known function must be analyzed and reported in the specification is not the standard for written description. Id.

Moreover, in contrast to the Examiner’s assertion, the claims do set forth functional properties for the modified MHC monomer. Specifically, the modified MHC monomer is required to bind the template peptide and assemble into a ternary complex with the template peptide and beta-2 microglobulin. Such functional requirements coupled with that which was known in the art with respect to the portions of the MHC that are responsible for interaction with template and beta-2 microglobulin allows the skilled artisan to envision the modified MHC monomers.

Thus, it is respectfully submitted that the claims are fully supported by the disclosure and that which was known in the art at the time of filing. Accordingly, reconsideration and withdrawal are respectfully requested.

**II. Rejections under 35 U.S.C. §112, Second Paragraph**

Claims 1-6, 9-14, 17-22, 25-31, 34-39, 42-47, 50, and 73-77 stand rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants note that this rejection as applied to claims 10, 12, 18, 19, 35, 37, 43, and 44 has been rendered moot by the cancellation herein of these claims. Applicants respectfully traverse the rejection as it applies to the pending claims.

Specifically, the Examiner asserts that claim 73 appears to be missing a portion of the claim and is missing a period at the end. Claim 73 has been amended herein to include a period at the end and to delete an apparently extraneous “and” at the end of item b). Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

The Examiner further asserts that the phrase “modified MHC monomer” as used in claims 1, 26, and 73 is allegedly unclear. Without acquiescing to the reasoning offered by the Examiner, this phrase has been amended herein to define modified MHC monomers with greater particularity. Thus, as presently amended, modified MHC monomers are HLA-A2 molecules further comprising beta-2 microglobulin and “maintain the ability to assemble into a ternary complex with the template MHC-binding peptide and beta-2 microglobulin.” Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

The Examiner further asserts that claims 73-77 are allegedly indefinite because the term “system” is not clear. It is respectfully submitted that the claims as written would be readily understood by the skilled artisan. Indeed the “system” is fully defined in the claim with respect to its component parts, i.e., an MHC monomer or modified MHC monomer having a template binding peptide bound thereto and a tracer binding peptide tagged with a detectable label. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

**III. Rejection under 35 U.S.C. §102**

Claims 1, 2, 4, 5, 10-12, 18-22, 25-27, 29, 30, 35-37, 43-47, and 50 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Celis *et al.* (*PNAS* 91:2105-9, 1994) (hereinafter, “Celis”) as evidenced by Henderson *et al.* (*PNAS* 90:10275-9, 1993) (hereinafter, “Henderson”) and Springfrog ([springfrog.com/converter/temperature.htm](http://springfrog.com/converter/temperature.htm), 2007). Applicants note that this rejection as applied to claims 10, 12, 18, 19, 35, 37, 43, and 44 has been rendered moot by the cancellation herein of these claims. Applicants respectfully traverse the rejection as it applies to the pending claims.

Specifically, the Examiner asserts that Celis teaches “an MHC peptide binding assay for determining relative affinity using HLA-A1 MHC class I molecules with a labeled standard peptide of 9 amino acid residues in length and a competitor test peptide (in about the 10  $\mu$ M to 1 nM range, and of 9 to 10 amino acid residues in length), for 2 days at room temperature in the presence of exogenous  $\beta$ 2m” (Office Action at page 4). Contrary to the Examiner’s assertion, it is respectfully submitted that Celis does not disclose all of the required elements of claims.

The present invention is based on the discovery that “a solution-based competition peptide exchange assay can be used to rapidly compare and quantify the binding affinity of peptides of unknown binding properties for MHC heavy chain monomers and modified MHC monomers” (specification at paragraph 0018). Moreover, the present invention provides a method in which “using a third labeled peptide of known affinity in a competition solution-based assay, the exchange reaction can be measured by observing the degree to which the labeled peptide out competes the test peptide” (specification at paragraph 0018). Thus, the invention, as defined by claim 1, as presently amended, requires three distinct MHC binding peptides (i.e., a template peptide bound to the MHC monomer, a competitor peptide, and a labeled tracer peptide).

In contrast, Celis, teaches only two peptides (i.e., a radiolabeled standard peptide having a known sequence and a test peptide). Indeed, the Examiner acknowledges that the

reference “does not explicitly teach ‘at least one MHC monomer...having bound thereto a template MHC-binding peptide” (Office Action at page 5). That is, the reference does not teach the template peptide. Moreover, it is respectfully submitted that because of the method used to purify the MHC monomer in Celis, it is likely that there is not a bound template peptide. Specifically, the MHC monomers taught in Celis are purified by a method that includes affinity chromatography with elution at pH 11.5 (see Celis at p. 2106, col. 1, 3rd full paragraph and cited reference 13, *i.e.*, Ruppert *et al.*, *Cell* 74:929-37, 1993, copy attached). Such treatment is consistent with there not being a bound template because, it has been shown in the literature, “alkaline-treatment at pH 11.7 ... dissociates most HLA class I proteins into  $\alpha$  and  $\beta$  chains and releases the bound endogenous peptides” (emphasis added) (Chersi *et al.*, *Human Immunol* 61:1298-1306, 2000, copy attached).

Furthermore, the presently claimed methods differ from the method of Celis with respect to the MHC monomer. Specifically, the present claims require that the MHC monomer is an HLA-A2 monomer or modified HLA-A2 monomer. In contrast, Celis discloses a method employing HLA-A1 monomers. At a minimum, these elements are not disclosed by Celis and therefore, Celis does not anticipate the present claims.

Moreover, it is respectfully submitted that the components of the claimed assay are significantly different from the those of the method described in Celis is evidenced by a significant difference in the length of time required for incubation of the MHC monomer and binding peptides in the presently claimed method, as compared to the Celis method. Specifically, the method of the present claims can be performed in as little as 2 hours (see e.g., paragraph 0075), whereas the method disclosed in Celis requires 48 hours. This difference in time could be explained in part by the monomers of the Celis method not having bound template peptide, thus requiring the folding and assembly of ternary structures and increasing the required incubation time.

For at least the reasons above, it is respectfully submitted that the Celis reference does not anticipate the present methods. Accordingly, reconsideration and withdrawal are respectfully requested.

**IV. Rejection under 35 U.S.C. §103**

Claims 1, 6, 9, 26, 31, 73, 74, and 77 stand rejected under 35 U.S.C. 103(a) as allegedly obvious in view of Celis *et al.* (supra) in view of US Patent No. 5,734,023 (hereinafter “the ‘023 patent”) and Gerritsma *et al.* (*Blood* 98(11), part 1, pp404a-405a, abstract) (hereinafter “Gerritsma”). Applicants respectfully traverse this rejection as it applies to the pending claims.

The Office Action alleges that Celis teaches an MHC peptide binding assay for determining relative affinity using purified HLA-A1 MHC class I molecules incubated with a labeled standard peptide and a competitor peptide, but acknowledges that the reference does not teach that the tracer peptide has a detectable label that is a fluorophore (claims 6 and 31) such as a fluorescein (claims 9 and 34), nor does it teach a system for identifying an MHC-binding peptide (claims 73, 74, and 77).

It is respectfully submitted that the present claims are not obvious over Celis in view of the ‘023 patent and Gerritsma. As discussed above, Celis does not disclose all of the elements of independent claims 1 and 26. Moreover, the ‘023 patent and Gerritsma do not cure the deficiencies of Celis for the reasons discussed below.

As discussed above, Celis does not disclose the use of an assay utilizing three distinct MHC-binding peptides (i.e., a template peptide, a tracer peptide, and a competitor peptide), much less an assay in which the template and tracer peptides have recited relative affinities for the MHC monomer. Moreover, the assay disclosed in Celis requires a much longer incubation time of 48 hours (versus a minimum 2 hours in the present assay).

The ‘023 patent is relied on by the Examiner for the disclosure of the adding of an effector component (e.g., fluorescein) to an MHC/peptide molecule and formulating the

MHC molecule into diagnostic or therapeutic kits. However, the '023 patent fails to cure the deficiencies of Celis described above. Specifically, the binding assays provided in the '023 patent do not employ the three MHC-binding peptides as set forth in the present claims. Moreover, the incubation times of the assays taught in the '023 patent are consistent with Celis (i.e., 48 hours) and thus, do not cure this deficiency of Celis.

Gerritsma is relied on by the Examiner for the disclosure of a MHC binding peptide having a fluorescent label. However, the Gerritsma reference is merely an abstract and as such does not provide sufficient experimental detail (with respect to binding peptides and incubation time) to cure the deficiencies of Celis as discussed above. Indeed, Gerritsma is silent with regard to the use of three MHC binding peptides, as well as the assay conditions (e.g., incubation time).

Thus, the present claims are not obvious over over Celis in view of the '023 patent and Gerritsma because the references in combination do not provide all of the elements of the pending claims. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

**Conclusion**

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

The Commissioner is hereby authorized to charge \$640.00 as payment for the Petition for Two-Month Extension of Time fee (\$460.00) and the Information Disclosure Statement fee (\$180.00) to Deposit Account No. 07-1896. Additionally, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896.

Respectfully submitted,

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Attachments: Ruppert *et al.*, *Cell* 74:929-37, 1993  
Chersi *et al.*, *Human Immunol* 61:1298-1306, 2000